

Patent Claims

1. Conjugate, characterized by the formula (I)



in which

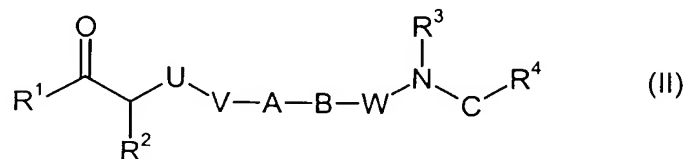
CT denotes a cytotoxic radical or a radical of a cytostatic or of a cytostatic derivative, which can additionally carry a hydroxyl, carboxyl or amino group,

LI is a linker group comprising 5 to 8 amino acid residues in the D or L configuration, which can each optionally carry protective groups,

Sp is absent or a carbonyl or a thiocarbonyl radical,

IA is a non-peptide radical addressing an $\alpha_v\beta_3$ integrin receptor, which is selected from the group consisting of

A) a radical of the formula (II)



in which

5 R^1 is OH, a substituted or unsubstituted alkoxy or cycloalkoxy radical, a substituted or unsubstituted aryloxy radical or a saturated or unsaturated, optionally substituted heterocycloxy radical, or optionally represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (II) is bonded to the rest of the conjugate;

10 R^2 is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical, an optionally substituted alkenyl radical or an optionally substituted alkynyl radical, via which the radical of the formula (II) is optionally bonded to the rest of the conjugate, or is $-NR^{2'}$, $-NR^{2'}SO_2R^{2''}$, $-NR^{2'}COOR^{2''}$, $-NR^{2'}COR^{2'}$, $-NR^{2'}CONR^{2'}$ or $-NR^{2'}CSNR^{2'}$;
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in which

20 $R^{2'}$ independently of one another is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical or a saturated or unsaturated, optionally substituted heterocyclic radical, or optionally represents a direct bond, via which the radical of the formula (II) is bonded to the rest of the conjugate;

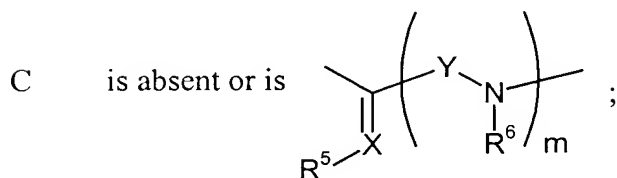
25 $R^{2''}$ is a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical or a saturated or unsaturated, optionally substituted heterocyclic radical, via which the radical of the formula (II) is optionally bonded to the
30 rest of the conjugate;

U is a direct bond or a substituted or unsubstituted alkylene group, via which the radical of the formula (II) is optionally bonded to the rest of the conjugate;

5 V is a substituted or unsubstituted alkylene group, $-NR^{2'}CO-$ or $-NR^{2'}SO_2-$, via which the radical of the formula (II) is optionally bonded to the rest of the conjugate;

10 A and B each independently of one another is a 1,3- or 1,4-bridged, optionally additionally substituted phenylene group;

W is a direct bond or a substituted or unsubstituted alkylene group;



15 R³ is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical, an alkylamine radical, an alkylamide radical or is bonded to one of R⁴, Y, R⁵ or R⁶, if present, with formation of an optionally substituted heterocyclic ring system, which includes the nitrogen atom to which R³ is bonded and can be saturated or unsaturated and/or can contain further heteroatoms;

25 R⁴ is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical, an alkylamine radical, an alkylamide radical or is bonded to one

of R^3 , Y, R^5 or R^6 , if present, with formation of an optionally substituted heterocyclic ring system which includes the nitrogen atom to which R^4 is bonded and can be saturated or unsaturated and/or can contain further heteroatoms, or optionally represents a direct bond, via which the radical of the formula (II) is bonded to the rest of the conjugate;

X is O, N or S;

m is 0 or 1;

Y is a direct bond or an optionally substituted alkylene or alkine group;

R^5 is absent, $-\text{NO}_2$, $-\text{CN}$, $-\text{COR}^{5'}$, $-\text{COOR}^{5'}$, or is bonded to one of R^3 , Y, R^4 or R^6 , if present, with formation of an optionally substituted carbocyclic or heterocyclic ring system which includes X and can be saturated or unsaturated and/or can contain further heteroatoms;

$R^{5'}$ is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical or a saturated or unsaturated, optionally substituted heterocyclic radical which can be saturated or unsaturated and/or can contain further heteroatoms;

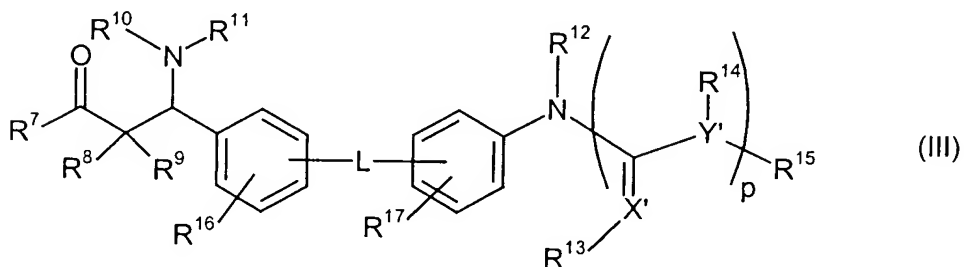
R^6 is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical, an alkylamine radical, an alkylamide radical or is bonded to one of R^3 , R^4 , Y or R^5 , if present, with formation of an optionally

substituted heterocyclic ring system which includes the nitrogen atom to which R^6 is bonded and can be saturated or unsaturated and/or can contain further heteroatoms;

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or

B) a radical of the formula (III)



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in which

R^7 is OH, a substituted or unsubstituted alkoxy or cycloalkoxy radical, a substituted or unsubstituted aryloxy radical or a saturated or unsaturated, optionally substituted heterocycloxy radical, or optionally represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (III) is bonded to the rest of the conjugate;

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R^8 is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical, an optionally substituted alkenyl radical, an optionally substituted alkynyl radical, a hydroxyl radical or an alkoxy radical or is bonded to R^9 with formation of an optionally substituted carbocyclic or heterocyclic ring system which includes the

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carbon atom to which R^8 is bonded and can optionally contain heteroatoms;

5 R^9 is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical, an optionally substituted alkenyl radical, an optionally substituted alkynyl radical, a hydroxyl radical or an alkoxy radical or is bonded to R^8 with formation of an optionally substituted carbocyclic or heterocyclic ring system which includes the carbon atom to which R^9 is bonded and can optionally contain heteroatoms;

10 R^{10} is $-SO_2R^{10'}$, $-COOR^{10''}$, $-COR^{10'}$, $-CONR^{10'}_2$ or $-CS-NR^{10'}_2$, or represents a direct bond via which the radical of the formula (III) is optionally bonded to the rest of the conjugate;

15 $R^{10'}$ independently of one another is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical or a saturated or unsaturated, optionally substituted heterocyclic radical, via which the radical of the formula (III) is optionally bonded to the rest of the conjugate;

20 $R^{10''}$ is a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical or a saturated or unsaturated, optionally substituted heterocyclic radical, via which the radical of the formula (III) is optionally bonded to the rest of the conjugate;

25 R^{11} is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical or a substituted or unsubstituted aryl radical.

R^{16} is hydrogen, CN, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted alkoxy radical or a halogen atom;

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R^{17} is hydrogen, CN, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted alkoxy radical or a halogen atom;

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L is $-(CH_2)_nNH SO_2(CH_2)_o-$, $-(CH_2)_nSO_2NH(CH_2)_o-$,
 $-(CH_2)_nNH-CO(CH_2)_o-$, $-(CH_2)_nCONH(CH_2)_o-$,
 $-(CH_2)_nOCH_2(CH_2)_o-$, $-(CH_2)_nCH_2O(CH_2)_o-$,
 $-(CH_2)_nCOO(CH_2)_o-$, $-(CH_2)_nOOC-(CH_2)_o-$,
 $-(CH_2)_nCH_2CO(CH_2)_o-$, $-(CH_2)_nCOCH_2(CH_2)_o-$, $-NHCONH-$,
 $-(CH_2)_nSCH_2(CH_2)_o-$, $-(CH_2)_nCH_2S(CH_2)_o-$,
 $-(CH_2)_nCH_2SO(CH_2)_o-$, $-(CH_2)_nSOCH_2(CH_2)_o-$,
 $-(CH_2)_nCH_2SO_2(CH_2)_o-$ or $-(CH_2)_nSO_2CH_2(CH_2)_o-$,

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where n and o each is an integer of 0 or 1 and $n + o \leq 1$;

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R^{12} is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical or is bonded to one of R^{13} , R^{14} or R^{15} , if present, with formation of an optionally substituted heterocyclic ring system which includes the nitrogen atom, to which R^{12} is bonded and can be saturated or unsaturated and/or can contain further heteroatoms;

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X' is N, O or S;

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p is 0 or 1;

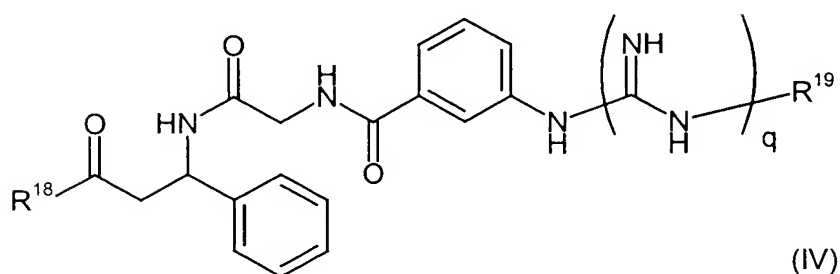
- 5 R^{13} is absent, is -H, a substituted or unsubstituted alkyl or cycloalkyl radical, -NO₂, -CN, -COR^{13'}, -COOR^{13'}, or is bonded to one of R¹², R¹⁴ or R¹⁵ with formation of an optionally substituted heterocyclic ring system which includes X' and can be saturated or unsaturated and/or can contain further heteroatoms;
- 10 $R^{13'}$ is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical or a saturated or unsaturated, optionally substituted heterocyclic radical which can be saturated or unsaturated and/or can contain further heteroatoms;
- 15 Y' is N or S;
- 20 R^{14} is absent, hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical or is bonded to one of R¹², R¹³ or R¹⁵, if present, with formation of an optionally substituted heterocyclic ring system which includes the nitrogen atom to which R¹⁴ is bonded and can be saturated or unsaturated and/or can contain further heteroatoms;
- 25 R^{15} is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical or is bonded to one of R¹², R¹³ or R¹⁴, if present, with formation of
- 30 an optionally substituted heterocyclic ring system which includes the nitrogen atom to which R¹⁵ is bonded and can be

saturated or unsaturated and/or can contain further hetero-atoms, or optionally represents a direct bond via which the radical of the formula (III) is bonded to the rest of the conjugate;

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or

C) a radical of the formula (IV)



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in which

R^{18} is OH, a substituted or unsubstituted alkoxy or cycloalkoxy radical, a substituted or unsubstituted aryloxy radical or a saturated or unsaturated, optionally substituted heterocycloxy radical, or optionally represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (IV) is bonded to the rest of the conjugate;

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q is 0 or 1;

R^{19} is hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical, a saturated or unsaturated, optionally substituted heterocyclic radical, an alkylamine radical, an alkylamide radical, or optionally

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represents a direct bond, via which the radical of the formula (IV) is bonded to the rest of the conjugate;

and their physiologically acceptable salts and stereoisomers.

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2. Conjugate according to Claim 1, characterized in that

LI is a linker group having the formula

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-AA1-AA2-AA3-AA4-AA5-AA6-AA7-AA8-

wherein at least 5 of the radicals AA1 to AA8 are present, AA1 is bonded to the radical CT and

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AA1 is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, glutamate, aspartate, serine, lysine, ornithine and phenylalanine;

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AA2 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, valine, phenylalanine, tyrosine, threonine, serine, isoleucine, lysine, glutamate, histidine, glycine, arginine, asparagine, glutamine, S-methyl-cysteine, methionine, arginine, aspartate, tryptophane, proline, ornithine and leucine, and can optionally carry protective groups,

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AA3 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, valine, phenylalanine, tyrosine, serine, isoleucine, lysine, glutamate, histidine, glycine, arginine, aspartate, trypto-

phane, proline, ornithine, methionine, S-methyl-cysteine, norvaline and leucine, and can optionally carry protective groups,

5 AA4 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, cysteine and norvaline;

10 AA5 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, tyrosine, glutamine, asparagine, proline, methionine, phenylalanine and cysteine;

15 AA6 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, glutamine, asparagine, aspartate and proline;

20 AA7 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, γ -amino-butyric acid, aspartate, glutamate, lysine and proline;

25 AA8 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, lysine, proline and γ -aminobutyric acid;

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and the other radicals CT, Sp and IA are as defined in claim 1.

3. Conjugate according to claim 2, characterized in that

LI is a linker group having the formula

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-AA1-AA2-AA3-AA4-AA5-AA6-AA7-AA8-

wherein 5 to 7 of the radicals AA1 to AA8 are present, AA1 is bonded to the radical CT and

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AA1 is valine, glycine, leucine, histidine;

AA2 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, phenylalanine, serine, isoleucine, glutamate, asparagine, glutamine, histidine, glycine, aspartate, tryptophane, proline, and leucine, and can optionally carry protective groups,

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AA3 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, phenylalanine, serine, isoleucine, norvaline, S-methylcysteine, methionine, glutamate, histidine, glycine, aspartate, tryptophane, and leucine, and can optionally carry protective groups,

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AA4 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, leucine, cysteine and norvaline, and can optionally carry protective groups,

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AA5 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, histidine, glutamine, phenyl-alanine, isoleucine, and methionine,

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AA6 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, proline, glutamine, methionine, and leucine;

10

AA7 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, leucine, aspartate, histidine, γ -aminobutyric acid and proline;

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AA8 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, proline and γ -aminobutyric acid ;

and the other radicals CT, Sp and IA are as defined in claim 1.

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4. Conjugate according to claim 2 or 3, characterized in that

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CT is camptothecin or a camptothecin derivative, which can be bonded to the rest of the conjugate via the C20-OH group, or doxorubicine, or quinolone a;

LI is as defined in claim 2 or 3;

Sp is absent, or is a carbonyl or a thiocarbonyl radical,

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IA denotes a non-peptide radical of the formula (II) addressing an $\alpha_v\beta_3$ integrin receptor,

in which

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R^1 is OH, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, cyclopropoxy, cyclopropylmethoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, phenoxy, benzyloxy, tolyloxy or a substituted derivative thereof, or optionally represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (II) is bonded to the rest of the conjugate;

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R^2 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, an optionally substituted alkenyl radical or an optionally substituted alkynyl radical, via which the radical of the formula (II) is optionally bonded to the rest of the conjugate, or is $-NR^{2'}_2$, $-NR^{2'}SO_2R^{2''}$, $-NR^{2'}COOR^{2''}$, $-NR^{2'}COR^{2'}$, $-NR^{2'}CONR^{2'}_2$ or $-NR^{2'}CSNR^{2'}_2$,

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in which

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$R^{2'}$ independently of one another is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, or optionally represents a direct bond via which the radical of the formula (II) is bonded to the rest of the conjugate;

30

$R^{2''}$ is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, -C₆H₂(CH₃)₃, 3-aminophenyl, 4-aminophenyl, 2-chlorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 2,5-dichlorophenyl, 4-trifluoromethylphenyl, camphor-10-yl, 4-t-butylphenyl, 2,5-dimethylphenyl, 3-chlorophenyl, 2-methoxy-5-methylphenyl, 2,3,5,6-tetramethylphenyl, 2,3-dichlorophenyl, 2,6-dichlorophenyl, 2-naphthyl, 3-trifluoromethylphenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-chloro-6-methylphenyl, 2-chloro-4-fluorophenyl, 2,5-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3-chloro-6-methoxyphenyl, 2-trifluoromethylphenyl, 2-alkylsulphonylphenyl, 2-arylsulphonylphenyl, 3-(N-acetyl-6-methoxy)aniline or 8-quinolinyl, via which the radical of the formula (II) is optionally bonded to the rest of the conjugate;

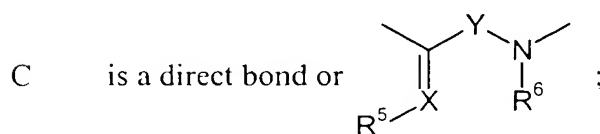
U is a direct bond,

V is an optionally substituted C₁₋₅-alkylene group, via which the radical of the formula (II) is optionally bonded to the rest of the conjugate;

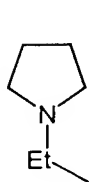
A is a 1,3- or 1,4-bridged phenylene group which is unsubstituted or contains at least one alkoxy radical;

B is a 1,3- or 1,4-bridged phenylene group which is unsubstituted or contains at least one alkyl radical;

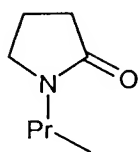
W is a direct bond or an optionally substituted C₁₋₄-alkylene group;



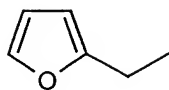
5 R^3 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C_{1-4} -alkylamino- C_{1-4} -alkyl, C_{1-4} -dialkylamino- C_{1-4} -alkyl, amino- C_{1-4} -alkyl, C_{1-4} -alkyloxy- C_{1-4} -alkyl,



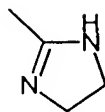
(a1)



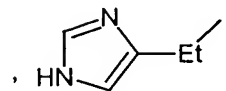
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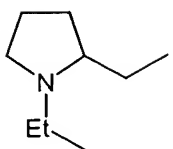
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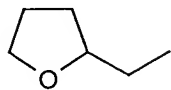
(a4)



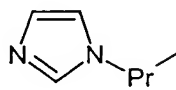
(a5)



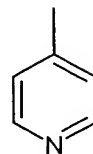
(a6)



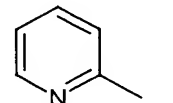
(a7)



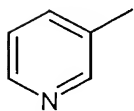
(a8)



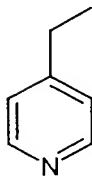
(a9)



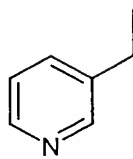
(a10)



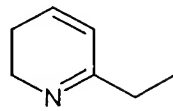
(a11)



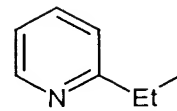
(a12)



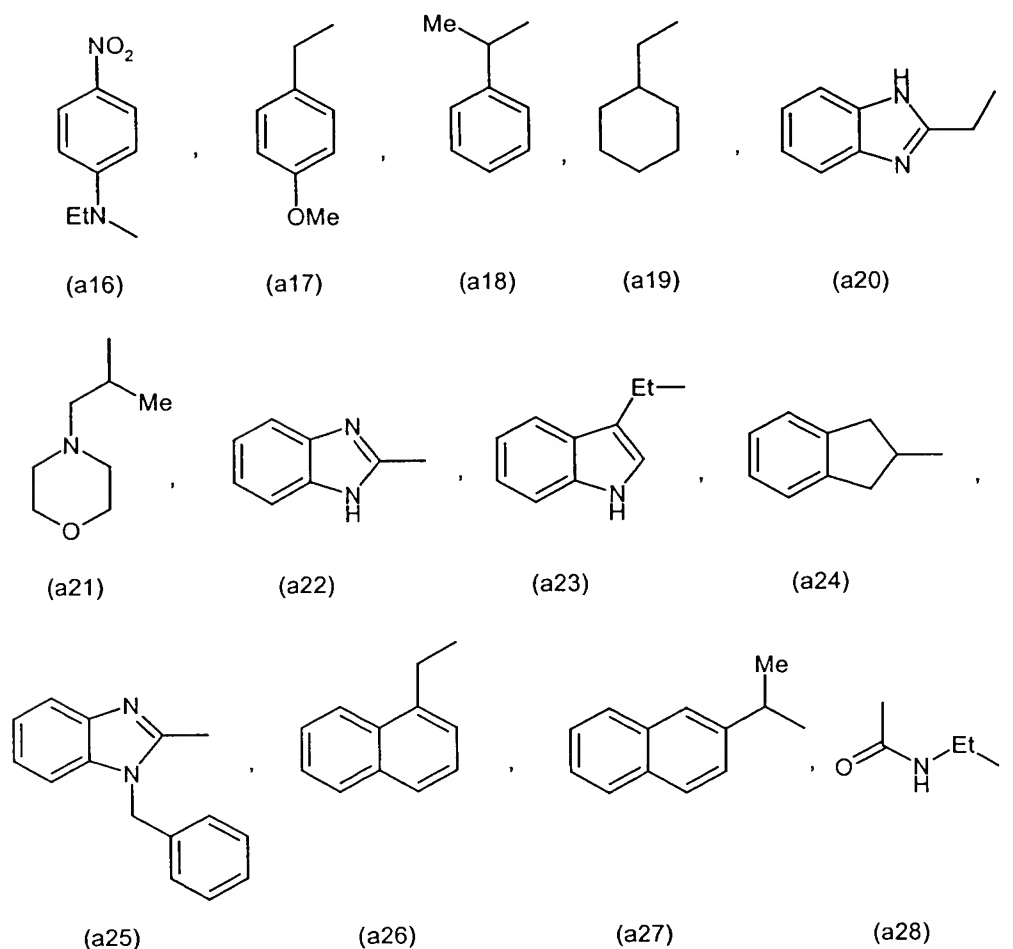
(a13)



(a14)



(a15)



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or is bonded to one of R^4 , Y, R^5 or R^6 , if present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system, which includes the nitrogen atom to which R^3 is bonded and can be saturated or unsaturated and/or can contain further heteroatoms;

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R^4 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C_{1-4} -alkylamino- C_{1-4} -alkyl, C_{1-4} -dialkylamino- C_{1-4} -alkyl, amino- C_{1-4} -alkyl, C_{1-4} -alkyloxy- C_{1-4} -alkyl, one of the radicals (a1) to (a28) or is bonded to one of R^3 , Y, R^5 or R^6 , if

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present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system which includes the nitrogen atom to which R^4 is bonded and can be saturated or unsaturated and/or can contain further heteroatoms, or optionally represents a direct bond via which the radical of the formula (II) is bonded to the rest of the conjugate;

X is O, N or S;

Y is a direct bond or a substituted or unsubstituted methylene or methine group;

R^5 is absent, is $-NO_2$, $-CN$, $-COR^{5'}$, $-COOR^{5'}$ or is bonded to one of R^3 , Y, R^4 or R^6 , if present, with formation of an optionally substituted carbocyclic or heterocyclic 4- to 6-membered ring system which includes X and which can be saturated or unsaturated and/or can contain further heteroatoms;

$R^{5'}$ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, tolyl or a substituted derivative thereof;

R^6 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C_{1-4} -alkylamino- C_{1-4} -alkyl, C_{1-4} -dialkylamino- C_{1-4} -alkyl, amino- C_{1-4} -alkyl, C_{1-4} -alkyloxy- C_{1-4} -alkyl, one of the radicals (a1) to (a28) or is bonded to one of R^3 , Y, R^4 or R^5 , if present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system which includes the nitrogen atom to which

R^6 is bonded and can be saturated or unsaturated and/or can contain further heteroatoms.

5. Conjugate according to Claim 4, characterized in that
- 5 R^1 represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (II) is bonded to the rest of the conjugate;
- 10 and the other radicals of the formula (II) are as defined in Claim 4.
6. Conjugate according to Claim 4, characterized in that
- 15 R^4 represents a direct bond, via which the radical of the formula (II) is bonded to the rest of the conjugate;
- and the other radicals of the formula (II) are as defined in Claim 4.
7. Conjugate according to Claim 4, characterized in that the radical of the
- 20 formula (II) is linked to the rest of the conjugate via a radical in the α - or β -position relative to the carboxyl group,
- and the other radicals of the formula (II) are as defined in Claim 4.
- 25 8. Conjugate according to Claim 2 or 3, characterized in that
- CT is camptothecin or a camptothecin derivative, which can be linked to the rest of the conjugate via the C20-OH group, or doxorubicine or quinolone a;
- 30 LI is as defined in claim 2 or 3;

Sp is absent, or a carbonyl or a thiocarbonyl radical,

IA is a non-peptide radical of the formula (II) addressing an $\alpha_v\beta_3$ integrin receptor,

5

in which

10

R¹ is OH, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, cyclopropoxy, cyclopropylmethoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, phenoxy, benzyloxy, tolyloxy or a substituted derivative thereof, or optionally represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (II) is bonded to the rest of the conjugate;

15

20

R² is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, 4-aminobenzyl, tolyl, phenylethyl, a substituted derivative such as 4-aminobenzyl or a saturated or unsaturated, optionally substituted heterocyclic analogue thereof, an optionally substituted alkenyl radical, an optionally substituted alkynyl radical, via which the radical of the formula (II) is optionally bonded to the rest of the conjugate;

25

30

U is a direct bond or an optionally substituted C₁₋₃-alkylene group such as -CH(C₆H₄-3-NH)- or -CH(C₆H₄-4-NH)-, via which the radical of the formula (II) is optionally bonded to the rest of the conjugate;

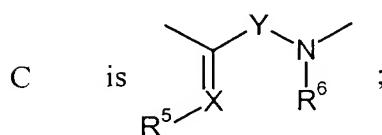
V is $-NR^{20}CO-$ or $-NR^{20}SO_2-$;

R^{20} is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, tolyl, phenylethyl, phenylpropyl, phenoxyethyl or a substituted derivative thereof;

A is a 1,3- or 1,4-bridged phenylene group which is unsubstituted or contains at least one alkoxy radical;

B is a 1,3- or 1,4-bridged phenylene group which is unsubstituted or contains at least one alkyl radical;

W is a direct bond or an optionally substituted C_{1-3} -alkylene group;



R^3 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C_{1-4} -alkylamino- C_{1-4} -alkyl, C_{1-4} -dialkylamino- C_{1-4} -alkyl, amino- C_{1-4} -alkyl, C_{1-4} -alkyloxy- C_{1-4} -alkyl, one of the radicals (a1) to (a28) or is bonded to one of R^4 , Y or R^6 , if present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system, which includes the nitrogen atom to

which R^3 is bonded, and can be saturated or unsaturated and/or can contain further heteroatoms;

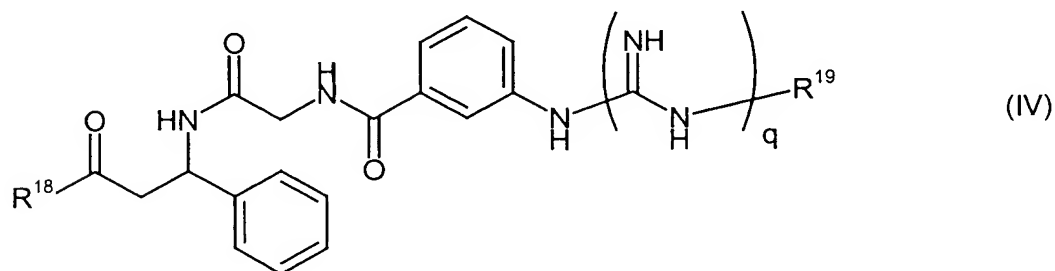
5 R^4 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C_{1-4} -alkylamino- C_{1-4} -alkyl, C_{1-4} -dialkylamino- C_{1-4} -alkyl, amino- C_{1-4} -alkyl, C_{1-4} -alkyloxy- C_{1-4} -alkyl, one of the radicals (a1) to (a28) or is bonded to one of R^3 , Y or R^6 , if present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system, which includes the nitrogen atom to which R^4 is bonded and can be saturated or unsaturated and/or can contain further heteroatoms, or optionally represents a direct bond via which the radical of the formula (II) is bonded to the rest of the conjugate;

20 X is O or S;

Y is a direct bond or a substituted or unsubstituted methylene or methine group;

25 R^5 is absent;

30 R^6 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C_{1-4} -alkylamino- C_{1-4} -alkyl, C_{1-4} -dialkylamino- C_{1-4} -alkyl, amino-



where the radicals in the formula (IV) have the meaning defined above.

5 The terminal carboxyl unit can, if the linkage to the rest of the conjugate does not take place via this, be present as a free carboxylic acid or as an ester. In the case in which the terminal carboxyl unit is esterified, fundamentally all carboxylic esters obtainable by conventional processes, such as the corresponding alkyl esters, cycloalkyl esters, aryl esters and heterocyclic analogues thereof can be used
10 according to the invention, where alkyl esters, cycloalkyl esters and aryl esters are preferred and the alcoholic radical can carry further substituents. Particularly preferred C₁₋₆-alkyl esters are those such as the methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, isopentyl ester, neopentyl ester, hexyl ester, cyclopropyl ester, cyclopropylmethyl ester, cyclobutyl ester, cyclopentyl ester, cyclohexyl ester, or aryl esters such as the phenyl ester, benzyl ester or tolyl ester.

The radicals of the formula (IV) according to the invention are preferably used in a form in which the terminal carboxyl unit is present as the free carboxylic acid.

20 The radicals of the formula (IV) according to the invention can contain a terminal guanidine or amino unit. The radical R¹⁹ here can be hydrogen, a substituted or unsubstituted alkyl or cycloalkyl radical, a substituted or unsubstituted aryl radical or a saturated or unsaturated, optionally substituted heterocyclic radical. A substituent is preferred here which is selected from the group consisting of hydrogen, a C₁₋₆-alkyl
25 such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl or hexyl, a C₃₋₇-cycloalkyl such as, for example, cyclopropyl,

5 C₁₋₄-alkyl, C₁₋₄-alkyloxy-C₁₋₄-alkyl, one of the radicals (a1) to (a28) or is bonded to one of R³, Y or R⁴, if present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system which includes the nitrogen atom to which R⁶ is bonded, and can be saturated or unsaturated and/or can contain further heteroatoms.

9. Conjugate according to Claim 8, characterized in that

10 R¹ represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (II) is bonded to the rest of the conjugate;

and the other radicals of the formula (II) are as defined in Claim 8.

15

10. Conjugate according to Claim 8, characterized in that

R⁴ represents a direct bond, via which the radical of the formula (II) is bonded to the rest of the conjugate;

20

and the other radicals of the formula (II) are as defined in Claim 8.

11. Conjugate according to Claim 8, characterized in that

25 the radical of the formula (II) is linked to the rest of the conjugate via a radical in the α - or β -position relative to the carboxyl group;

and the other radicals of the formula (II) are as defined in Claim 8.

30

12. Conjugate according to Claim 2 or 3, characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

LI is as defined in claim 2 or 3;

Sp is absent, or a carbonyl or a thiocarbonyl radical,

IA is a non-peptide radical of the formula (III) addressing an $\alpha_v\beta_3$ integrin receptor,

in which

R^7 is OH, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, cyclopropoxy, cyclopropylmethoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, phenoxy, benzyloxy, tolyloxy or a substituted derivative thereof, or optionally represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (III) is bonded to the rest of the conjugate;

R^8 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, benzyl, tolyl or a substituted derivative thereof, -OH, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, benzyloxy or is bonded to R^9 with formation of an optionally substituted 3- to 6-membered carbocyclic or heterocyclic ring system, which includes the carbon atom to which R^8 is bonded and can optionally contain heteroatoms;

R^9 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, benzyl, tolyl or a substituted derivative thereof, -OH, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy or is bonded to R^8 with formation of an optionally substituted 3- to 6-membered carbocyclic or heterocyclic ring system which includes the carbon atom to which R^9 is bonded and can optionally contain heteroatoms;

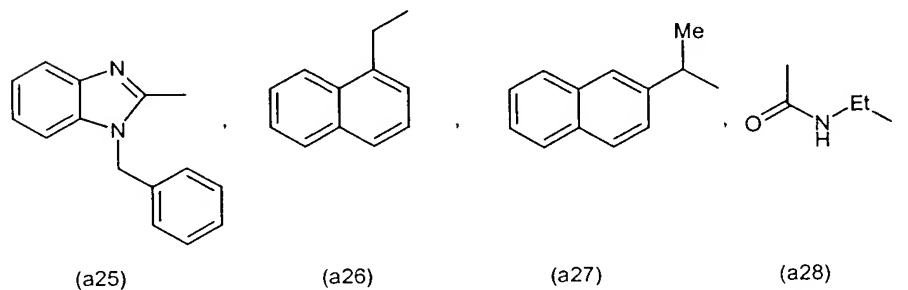
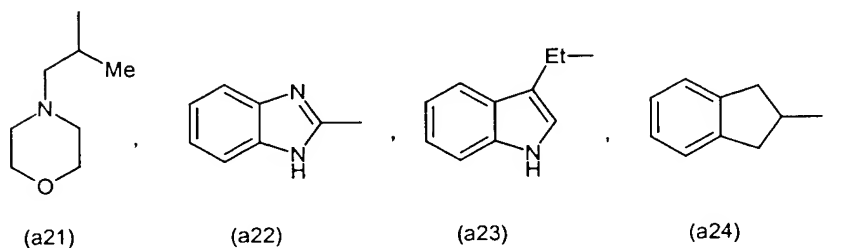
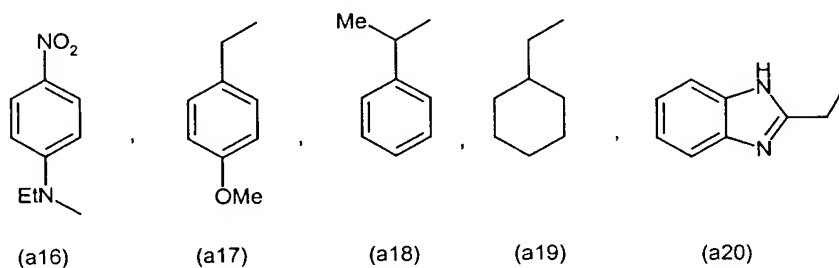
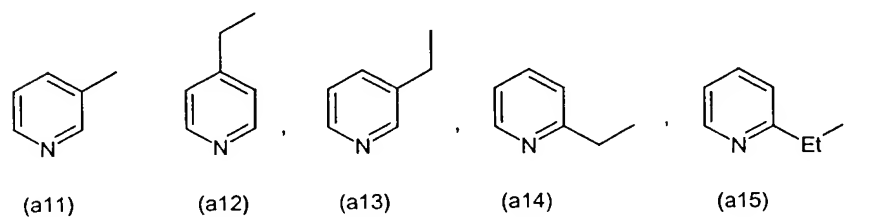
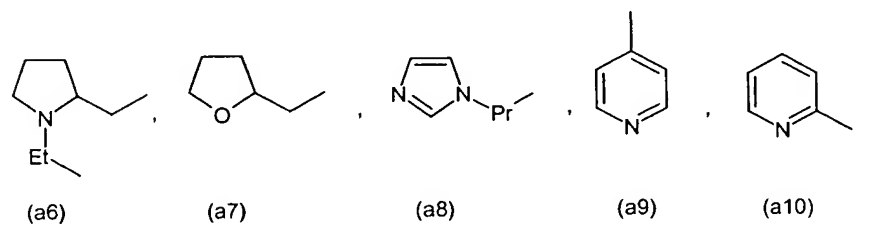
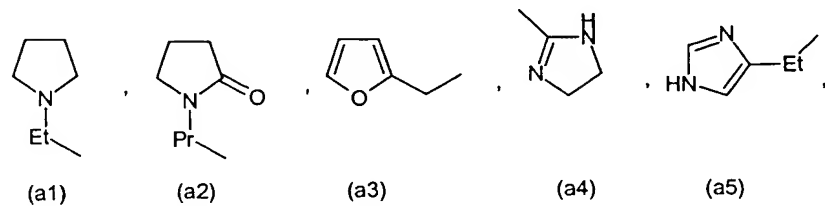
R^{10} is $SO_2R^{10'}$, $-COOR^{10'}$, $-COR^{10'}$, $-CONR^{10'}_2$ or $-CSNR^{10'}_2$ or represents a direct bond, via which the radical of the formula (III) is optionally bonded to the rest of the conjugate;

$R^{10'}$ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, benzyl, tolyl or a substituted derivative thereof, $-C_6H_2(CH_3)_3$, $-C_6(CH_3)_5$, $-CH_2C_6H_2(CH_3)_3$, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2,5-dichlorophenyl, 3,5-dichlorophenyl, 2,6-dichlorophenyl, 4-chlorophenylmethyl, 2,4-dichlorophenylmethyl, 2,6-dichlorophenylmethyl, 3-aminophenyl, 4-aminophenyl, 2-methoxycarbonylphenylmethyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3,5-bis(trifluoromethyl)phenyl, 4-trifluoromethoxyphenyl, phenylmethyl, 2-acetamido-4-methylthiazol-5-yl, phenylethyl, 1-phenylpropyl, (S)-(+)-camphor-10-yl, (R)-(-)-camphor-10-yl, 2-phenylethenyl, 2-thiophenyl, 4-methoxyphenyl, 3,5-dimethoxyphenyl, 3-methylphenyl, 4-methylphenyl, 4-t-butylphenyl, 4-propylphenyl, 2,5-dimethylphenyl, 2-methoxy-5-methylphenyl, 2,3,5,6-

tetramethylphenyl, 1-naphthyl, 2-naphthyl, 4-fluoro-phenyl, 2,4-difluorophenyl, 2-chloro-6-methylphenyl, 2-chloro-4-fluorophenyl, 2,5-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3-chloro-6-methoxyphenyl, 2-trifluoromethylphenyl, 2-alkylsulphonylphenyl, 2-arylsulphonylphenyl, 3-(N-acetyl-6-methoxy)aniline, 4-acetamidophenyl, 2,2,2-trifluoroethyl, 5-chloro-3-methylbenzothiazol-2-yl, N-meth-oxycarbonyl-piperidin-3-yl, thiophen-2-yl, isoxazol-5-yl, ethoxy, 2-chloropyridin-3-yl, pyridin-3-yl, benzyloxy, 5-methylisoxazol-3-yl, 1-adamantyl, 4-chlorophenoxymethyl, 2,2-dimethylethenyl, 2-chloropyridine-5-methyl, 5,7-dimethyl-1,3,4-triazaindolizin-2-yl, (S)-camphan-1-yl, (R)-camphan-1-yl or 8-quinolinyl;

$R^{10''}$ is a C_{1-6} -alkyl radical, a C_{3-7} -cycloalkyl radical, a substituted or unsubstituted aryl radical or a saturated or unsaturated, optionally substituted heterocyclic radical, via which the radical of the formula (III) is optionally bonded to the rest of the conjugate;

R^{11} is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C_{1-4} -alkylamino- C_{1-4} -alkyl, C_{1-4} -dialkylamino- C_{1-4} -alkyl, amino- C_{1-4} -alkyl, C_{1-4} -alkyloxy- C_{1-4} -alkyl, dialkylamino- C_{1-4} -alkyl, amino- C_{1-4} -alkyl, C_{1-4} -alkyloxy- C_{1-4} -alkyl or



R¹⁶ is hydrogen, CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclo-

propyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, methoxy, trifluoromethoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy, fluorine, chlorine, bromine or iodine;

5 R^{17} is hydrogen, CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, methoxy, trifluoromethoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy, fluorine, chlorine, bromine or iodine;

10 L is $-NHSO_2-$, $-CH_2NHSO_2-$, $-NHSO_2CH_2-$, $-SO_2NH-$, $-CH_2SO_2NH-$, $-SO_2NHCH_2-$, $-NHCO-$, $-CH_2NHCO-$, $-NHCOCH_2-$, $-CONH-$, $-CH_2CONH-$, $-CONHCH_2-$, $-OCH_2-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2O-$ or $-CH_2CH_2O-$;

15 R^{12} is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C_{1-4} -alkylamino- C_{1-4} -alkyl, C_{1-4} -dialkylamino- C_{1-4} -alkyl, amino- C_{1-4} -alkyl, C_{1-4} -alkyloxy- C_{1-4} -alkyl, one of the radicals (a1) to (a28) or is bonded to one of R^{13} , R^{14} or R^{15} , if present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system which includes the nitrogen atom to which R^{12} is bonded and can be saturated or
20
25
unsaturated and/or can contain further heteroatoms;

X' is N, O or S;

30 p is 0 or 1;

- 5 R^{13} is absent, is -H, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, -NO₂, -CN, -COR^{7'}, -COOR^{7'}, or is connected to one of R¹², R¹⁴ or R¹⁵ with formation of an optionally substituted carbocyclic or heterocyclic 4- to 6-membered ring system which includes X' and can be saturated or unsaturated and/or can contain further heteroatoms;
- 10 $R^{13'}$ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, benzyl, tolyl or a substituted derivative thereof;
- 15 Y' is N or S;
- 20 R^{14} is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C₁₋₄-alkylamino-C₁₋₄-alkyl, C₁₋₄-dialkylamino-C₁₋₄-alkyl, amino-C₁₋₄-alkyl, C₁₋₄-alkyloxy-C₁₋₄-alkyl, one of the radicals (a1) to (a28), or is bonded to one of R¹², R¹³ or R¹⁵, if present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system which includes the nitrogen atom to which R¹⁴ is bonded and can be saturated or unsaturated and/or can contain further heteroatoms; and
- 25
- 30 R^{15} is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropyl, cyclo-

propylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 5-methyl-2-hexyl, phenyl, benzyl, tolyl or a substituted derivative thereof, C₁₋₄-alkylamino-C₁₋₄-alkyl, C₁₋₄-dialkylamino-C₁₋₄-alkyl, amino-C₁₋₄-alkyl, C₁₋₄-alkyloxy-C₁₋₄-alkyl, one of the radicals (a1) to (a28) or is bonded to one of R¹², R¹³ or R¹⁴, if present, with formation of an optionally substituted heterocyclic 4- to 6-membered ring system which includes the nitrogen atom to which R¹⁵ is bonded and can be saturated or unsaturated and/or can contain further heteroatoms, and or optionally represents a direct bond via which the radical of the formula (III) is bonded to the rest of the conjugate.

13. Conjugate according to Claim 12, characterized in that

R⁷ represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (II) is bonded to the rest of the conjugate;

and the other radicals of the formula (III) are as defined in Claim 12.

14. Conjugate according to Claim 12, characterized in that

R¹⁵ represents a direct bond, via which the radical of the formula (III) is bonded to the rest of the conjugate;

and the other radicals of the formula (III) are as defined in Claim 12.

15. Conjugate according to Claim 12, characterized in that

the radical of the formula (III) is linked to the rest of the conjugate via a radical in the α - or β -position relative to the carboxyl group,

and the other radicals of the formula (III) are as defined in Claim 12.

5

16. Conjugate according to Claim 2 or 3, characterized in that

IA is a non-peptide radical of the formula (IV) addressing an $\alpha_v\beta_3$ integrin receptor,

10

wherein

R^{18} represents a direct bond or an atom from the group consisting of N, O and S, via which the radical of the formula (IV) is bonded to the rest of the conjugate;

15

and the other radicals are as defined in Claim 2 or 3.

17. Conjugate according to Claim 2 or 3, characterized in that

20

IA is a non-peptide radical of the formula (IV) addressing an $\alpha_v\beta_3$ integrin receptor,

wherein

25

R^{19} represents a direct bond, via which the radical of the formula (IV) is bonded to the rest of the conjugate;

and the other radicals are as defined in Claim 2 or 3.

30

18. Process for the preparation of conjugates according to Claim 1, comprising

[A] the reaction of a compound from the group of compounds of the formulae (II), (III) and (IV), which has a free or optionally activated carboxyl function,

5 with a compound of the formula (Ia) which has a free primary or secondary amino group



10 in which all radicals have the meaning indicated in Claim 1,

in the presence of a base;

or

15

[B] the reaction of a compound from the group of compounds of the formulae (II), (III) and (IV), which has a free primary or secondary amino function,

20 with a carbonic acid derivative such as, for example, phosgene, thiophosgene or a chloroformic acid ester, if appropriate in the presence of a base,

25 followed by the reaction with a compound of the formula (Ia) which has a free primary or secondary amino group



30 in which all radicals have the meaning indicated in Claim 1,

and

if appropriate the removal of protective groups and/or derivatization of nitrogen atoms present at preferred points of time in the preparation process and/or conversion of the compound obtained into the free acid and/or conversion of the compound obtained into one of its physiological salts by reaction with an inorganic or organic base or acid;

or

[C] the reaction of a compound from the group of compounds of the formulae (II), (III) and (IV), which contains a free primary or secondary amino function,

with a compound of the formula (Ia) which contains a free or optionally activated carboxyl function

CT-LI

(Ia)

in which all radicals have the meaning indicated in Claim 1,

in the presence of a base;

and

if appropriate the removal of protective groups and/or derivatization of nitrogen atoms present at preferred points in time in the preparation process and/or conversion of the compound obtained into the free acid and/or conversion of the compound obtained into one of its physiological salts by reaction with an inorganic or organic base or acid.

19. Process according to Claim 18, characterized in that several steps of the process are carried out on a solid phase.

5 20. Medicament, comprising at least one of the conjugates according to one of Claims 1 to 17.

21. Use of compounds according to one of Claims 1 to 17 for the production of medicaments for the treatment of carcinomatous disorders.